Bioactivity and Safety of IL13Ralpha2-Redirected Chimeric Antigen Receptor CD8+ T Cells in Patients with Recurrent Glioblastoma.

Journal: Clin Cancer Res

Publication Year: 2015

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PubMed link: 26059190

Funding Grants: Targeting glioma cancer stem cells with receptor-engineered self-renewing memory T cells

Public Summary:
Chimeric receptor (CAR)-expressing T cell therapies have demonstrated remarkable clinical success in the treatment of CD19+ blood cancers such as acute lymphoblastic leukemia. A major unmet goal for the field of CAR T cell immunotherapy is the successful application of this therapy to solid tumors. With this in mind, our group is focusing on developing CAR T cell therapies for the treatment of glioblastoma, a brain tumor that is essentially incurable with current standard-of-care therapies. Here we report the results of a first-in-human clinical trial evaluating first-generation CAR-expressing, T cell clones targeting the brain-tumor antigen IL13Rα2. These CAR T cells were administered after surgery into the tumor resection cavity of patients with glioblastoma. This therapy was well tolerated, with acceptable safety profiles observed for repeated CAR T cell delivery into the brain. Further, evidence for anti-glioma responses were observed in two of the three treated patients – with reduction in IL13Rα2-antigen expressing tumor cells in one, and enhanced tumor necrotic volume in another. This work is significant because it is the first to report the clinical use of CAR T cells for the treatment of brain tumors. Further, by demonstrating safety and bioactivity for IL13Rα2-specific CAR T cells, this study establishes a foundation for the application of adoptive T cell therapy for glioblastoma.

Scientific Abstract:
PURPOSE: A first-in-human pilot safety and feasibility trial evaluating chimeric antigen receptor (CAR)-engineered, autologous primary human CD8(+) cytotoxic T lymphocytes (CTL) targeting IL13Ralpha2 for the treatment of recurrent glioblastoma (GBM). EXPERIMENTAL DESIGN: Three patients with recurrent GBM were treated with IL13(E13Y)-zetakine CD8(+) CTL targeting IL13Ralpha2. Patients received up to 12 local infusions at a maximum dose of 10(8) CAR-engineered T cells via a catheter/reservoir system. RESULTS: We demonstrate the feasibility of manufacturing sufficient numbers of autologous CTL clones expressing an IL13(E13Y)-zetakine CAR for redirected HLA-independent IL13Ralpha2-specific effector function for a cohort of patients diagnosed with GBM. Intracranial delivery of the IL13-zetakine(+) CTL clones into the resection cavity of 3 patients with recurrent disease was well-tolerated, with manageable temporary brain inflammation. Following infusion of IL13-zetakine(+) CTLs, evidence for transient anti-glioma responses was observed in 2 of the patients. Analysis of tumor tissue from 1 patient before and after T-cell therapy suggested reduced overall IL13Ralpha2 expression within the tumor following treatment. MRI analysis of another patient indicated an increase in tumor necrotic volume at the site of IL13-zetakine(+) T-cell administration. CONCLUSIONS: These findings provide promising first-in-human clinical experience for intracranial administration of IL13Ralpha2-specific CAR T cells for the treatment of GBM, establishing a foundation on which future refinements of adoptive CAR T-cell therapies can be applied.